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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,926	07/31/2003	Carlo Riccardi	RICCARDI=1A	7576

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EXAMINER	
LIETO, LOUIS D	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,926	RICCARDI, CARLO	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1,2,5-16 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *3,4,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/31/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the Restriction was received on 4/25/2005. Claims 1-20 are pending in the instant application. Applicants elected the subject matter of group V, claims 3,4,17 and 18, drawn to a GILR transgenic mouse and a method for screening compounds having glucocorticoid-related effects using a GILR transgenic mouse, with traverse.

Response to Arguments

Applicant's election with traverse of the subject matter of group II in the reply filed on 4/25/2005is acknowledged. The traversal is on the ground(s) that the subject matter of group II, claim 19, drawn to a method of making a transgenic mouse should be rejoined with group V. Applicant's arguments are found to be persuasive. Therefore claim 19 will be joined to the subject matter of Group V for the purposes of examination. The new groups are: Group I drawn to claims 1, 2 and 20; Group II drawn to 3,4, and 17-19; Group III drawn to claims 5, 6, 9 11, 12, and 15; and Group III drawn to claims 7, 8, 10, 13, 14, 16.

Claims 1, 2, 5-16 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/25/2005.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3, 4 and 17-19 are under consideration.

Priority

It is noted the elected subject matter of the instant invention is drawn to a GILR transgenic mouse, a method of making said mouse, and a method for screening compounds having glucocorticoid-related effects using a GILR transgenic mouse. Parent application 09/403,861, issued as US Patent No. 6,833,348, does not provide an enabling disclosure for said mouse, a method of making or a method of using. Therefore the effective priority date for the claimed invention is its filing date of 7/31/2003.

Objections

Claims 3, 4 and 17-18 are objected to under 37 CFR 1.75(c), as being of improper dependent form because: claim 3 continues to depend in part on withdrawn claim 1. Claims 4, 17 and 18 depend on claim 3. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form.

Drawings

The drawings are objected to under 37 CFR 1.83(a) because they fail to show the banding patterns as described in the specification. Specifically, the resolution and clarity of Figures 1, 10 and 12 contain panels that are completely black, or where the resolution is so poor as to make it impossible to discern any banding patterns. Corrected drawing sheets are required in reply to the Office action to avoid abandonment of the application. Any amended replacement-drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure

must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the examiner does not accept the changes, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 4 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-5 and 7-13 are drawn to drawn to any transgenic mouse with a nucleic acid construct integrated in to its genome, said construct comprising any mammalian T-cell lineage specific, expression regulatory sequence operably linked to any GILR cDNA from any species, wherein said mouse expresses a GILR RNA or protein it its T cell lineage at an elevated level

compared to a non-transgenic mouse and the expression of GILR results in any alteration of the thymocyte subset composition and of caspase 3 activation. The claims encompass a genus of transgenic mice that are defined solely by the increased expression of any GILR RNA or protein in its T cell lineage.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The claimed genus contemplated in the specification encompasses a mouse comprising any nucleic acid construct that contains any T-cell specific regulatory sequence, such as a promoter, enhancer or repressor operably linked to any GILR cDNA from any species. This includes a range of transgenes with a vast number of different combinations of GILR cDNAs linked to regulatory sequences. The claimed genus of mice encompasses any mouse with a nucleic acid construct integrated into its genome that contains any mammalian T-cell lineage specific, expression regulatory sequence operably linked to any GILR cDNA from any species.

The factors to be considered when assessing possession of the claimed invention include disclosure of complete or partial structure, physical and/ or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claims is the requirement that the mouse have an elevated expression of GILR in its T-cell lineage, which results in any alteration of the T-cell subset composition and caspase-3 activation. The specification does not contemplate any specific GILR cDNA other than mouse or human GILR cDNA (specification pg. 29, pgph 29 and 30). The specification does not provide any guidance on the required efficiency of expression or at what developmental stage the expression regulatory sequences

must be active in order to alter the T-cell subset composition. The only alteration of the T-cell subset described in the specification is a significant decrease in CD4.sup.+CD8.sup.+ double positive, and increases in CD4.sup.-CD8.sup.- double negative, CD8.sup.+ single positive cells, and the CD4.sup.+ subpopulation, compared with a non-transgenic mouse (specification, pgph 312). The specification does not contemplate any other alteration of the T-cell subset composition such as changes in the gamma/delta positive T-cell subset or the CD56+/CD8+ T-cell subset. Further, the only specific T-cell lineage, expression regulatory sequences contemplated in the specification are the human CD2 promoter, the promoter of the lymphocyte-specific protein, tyrosinase Lck, the Ig VH1 promoter and the CD3-epsiolon promoter (specification pg. 63, pgph 215 bridge to pg. 64). The specification does not provide any guidance on any specific constructs, other than a transgene comprising a mouse GILR cDNA, 874 bp long, operably linked to a CD 2 promoter, that can alter the T-cell subset composition as disclosed. Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide adequate written description of the claimed a genus of transgenic mice that are defined solely by the increased expression of any GILR RNA or protein in its T cell lineage.

The Revised Interim Guidelines state, "when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement

as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for any a genus of transgenic mice that are defined solely by the increased expression of any GILR RNA or protein in its T cell lineage. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 3, 4 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse with a nucleic acid construct comprising an 874 bp mouse GILR cDNA operably linked to a human CD2 promoter and a human CD2 locus control region integrated into its genome, wherein said mouse expresses the GILR protein in its T-cell lineage at an elevated level, compared to a non-transgenic mouse, wherein the elevated level of GILR protein expression results in a significant decrease in CD4.sup.+CD8.sup.+ double positive, and increases in CD4.sup.-CD8.sup.- double negative, CD8.sup.+ single positive cells, and the CD4.sup.+ subpopulation, compared with a non-transgenic mouse, and increased caspase 3 activation; a method of using said transgenic mouse for screening compounds having glucocorticoid-related effects, comprising administering a

compound to said transgenic mouse and to a non-transgenic mouse and comparing the effects of the compound on the two mice; and a method of making said transgenic mouse comprising transferring a nucleic acid construct comprising an 874 bp mouse GILR cDNA operably linked to a human CD2 promoter and a human CD2 locus control region into a fertilized oocyte, transplanting said oocyte into a female mouse, allowing the zygote to develop to term, and selecting from the offspring a heterozygous transgenic mouse wherein the nucleic acid construct has integrated into its genome and the mouse expresses the GILR protein in its T-cell lineage at an elevated level, compared to a non-transgenic mouse, breeding said heterozygous transgenic mouse to a wild type mouse to obtain F1 progeny heterozygous for said transgene and breeding a heterozygous male mouse from the F1 progeny with a heterozygous female mouse from the F1 progeny and selecting for a mouse homozygous for the transgene, does not reasonably provide enablement for a transgenic mouse with any nucleic acid construct comprising any GILR cDNA from any species operably linked to any mammalian T-cell lineage specific expression regulatory sequence, wherein said mouse expresses GILR in its T cell lineage at an elevated level compared to a non-transgenic mouse and wherein the expression of GILR results in any alteration of the thymocyte subset composition and caspase-3 activation, a method of using any such transgenic mouse for screening compounds having glucocorticoid-related effects, or a method of making any such transgenic mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims encompass any transgenic mouse with any nucleic acid construct comprising any GILR cDNA from any species operably linked to any mammalian T-cell lineage specific

expression regulatory sequence, wherein said mouse expresses GILR in its T cell lineage at an elevated level compared to a non-transgenic mouse and wherein the expression of GILR results in any alteration of the thymocyte subset composition and caspase-3 activation.

The specification does not provide guidance on the construction of any transgenic mice other than a mouse comprising a nucleic acid construct comprising an 874 bp mouse GILR cDNA operably linked to a human CD2 promoter and a human CD2 locus control region integrated into its genome. The specification only discloses a human GILR sequence in addition to a mouse GILR sequence. The art does not teach that the GILR cDNA sequence was known from any species at the time of filing. Further, the specification does not disclose the construction of a transgene containing any GILR other than mouse GILR operably linked to any other regulatory sequences other than a CD promoter and a CD2 locus control region. The term regulatory sequence includes, promoters, enhancers, repressors and combinations thereof. It is unclear how a T-cell lineage repressor, alone, will lead to elevated levels of GLIR expression in a transgenic mouse. Further, the term "sequences" encompasses elements with complex developmental and T-cell specific expression patterns, such as the entire lck promoter system. This system contains a distal and proximal promoter, of which the proximal promoter contains a transcriptional repressor (Muise-Helmericks et al. (1995) J. Biol. Chem. 270:27538-27543; Abstract; pg. 27538, col. 1). This system regulates both the developmental and cell type expression of lck (pg. 27538, col. 1). Such a promoter system would not reasonably be predicated to produce the same disclosed phenotype as the instant mouse.

Further, the art of making a transgenic mouse is not predictable because of several factors. For example, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted,

" Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in non-targeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the "transgene" (see page 256, section 4 on transgene regulation and expression). Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given T-cell lineage specific, expression regulatory sequence can elevate the level of GILR transgene expression to a level sufficient to produce any alteration of the thymocyte subset composition and of caspase 3 activation. Further, the only thymocyte alteration disclosed in the specification that is attributable to the expression of the GILR transgene is a significant decrease in CD4.sup.+CD8.sup.+ double positive, and increases in CD4.sup.-CD8.sup.- double negative, CD8.sup.+ single positive cells, and the CD4.sup.+ subpopulation, compared with a non-transgenic mouse (specification, pgph 312). The specification does not disclose that any other transgene comprising a different mammalian T-cell lineage regulatory element and/or a different GILR cDNA from a species other than a mouse is capable of producing these same phonotypical alterations of the T cell subset. Given the lack of guidance in the specification on the construction of any transgenic mouse comprising any mammalian T-cell lineage specific, expression sequence operably linked to any GILR cDNA, the lack of guidance in the

specification that elevated levels of GILR expression in the T-cell lineage produces any other alteration in thymocyte subsets other than a decrease in CD4.sup.+CD8.sup.+ double positive cells, and increases in CD4.sup.-CD8.sup.- double negative, CD8.sup.+ single positive cells, and the CD4.sup.+ subpopulation, compared with a non-transgenic mouse, and the teachings in the art on the unpredictability of making any transgenic mouse, a skilled practitioner in the art would be unable to practice the invention as claimed, except as a transgenic mouse with a nucleic acid construct comprising an 874 bp mouse GILR cDNA operably linked to a human CD2 promoter and a human CD2 locus control region integrated into its genome, wherein said mouse expresses the GILR protein in its T-cell lineage at an elevated level, compared to a non-transgenic mouse, wherein the elevated level of GILR protein expression results in a significant decrease in CD4.sup.+CD8.sup.+ double positive, and increases in CD4.sup.-CD8.sup.- double negative, CD8.sup.+ single positive cells, and the CD4.sup.+ subpopulation, compared with a non-transgenic mouse, and increased caspase 3 activation; a method of using said transgenic mouse for screening compounds having glucocorticoid-related effects, comprising administering a compound to said transgenic mouse and to a non-transgenic mouse and comparing the effects of the compound on the two mice; and a method of making said transgenic mouse comprising transferring a nucleic acid construct comprising an 874 bp mouse GILR cDNA operably linked to a human CD2 promoter and a human CD2 locus control region into a fertilized oocyte, transplanting said oocyte into a female mouse, allowing the zygote to develop to term, and selecting from the offspring a heterozygous transgenic mouse wherein the nucleic acid construct has integrated into its genome and the mouse expresses the GILR protein in its T-cell lineage at an elevated level, compared to a non-transgenic mouse, breeding said heterozygous transgenic

mouse to a wild type mouse to obtain F1 progeny heterozygous for said transgene and breeding a heterozygous male mouse from the F1 progeny with a heterozygous female mouse from the F1 progeny and selecting for a mouse homozygous for the transgene, without extensive and undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4 and 17-19 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 refers to "an alteration of the thymocyte subset composition." The term "alteration" is vague and indefinite. "Alteration" could encompass any increase or decrease in the activity of a T cell, any change in T cell receptor expression, or any change in T-cell survival or proliferation. It is not clear from the body of the claim what constitutes an "alteration." Further, the specification does not define what is meant by alteration in terms of the possible changes in T-cell subset composition caused by elevated GILR transgene expression. As a result, the metes and bounds cannot be determined. Claims 4 and 17-19 on claim 3.

Claim 3 refers to "an expression regulatory sequence." The term "an expression regulatory sequence" is vague and indefinite. "an expression regulatory sequence" could encompass any promoter, enhancer, repressor, locus control region, alu repeat or any other sequence which binds transcription factors or impacts chromatin organization and accessibility. It is not clear from the body of the claim what constitutes an "an expression regulatory

sequence." Further, the specification does not define what is meant by an "expression regulatory sequence" in terms of the required attributes of such a sequence in order to be used in the transgene. Claims 4 and 17-19 on claim 3.

Claim 3 refers to "GILR." The term "GILR" is vague and indefinite. "GILR" is an acronym that could encompass multiple definitions in the art. It is not clear from the body of the claim what constitutes a "GILR." Further, it is not clear from the specification what the acronym GILR stands for. As a result, the metes and bounds cannot be determined. Claims 4 and 17-19 on claim 3.

No Claims Allowed

Examiners Comment

Please note that the closest prior art of record is exemplified by King et al. (King et al. (King et al. (1995) Immunity. 3:647-656). King et al teaches the construction of a transgenic mouse that expresses anti-sense transcripts to the glucocorticoid receptor under control of the lck-AGR plasmid (Abstract; pg. 654, materials and methods). Also note Delfino et al., which is the reference published by the inventor's group and describes the claimed mouse {Delfino et al. (2004) Immunobiology. 104:4134-4141}.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the

organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Dr. Louis D. Lieto
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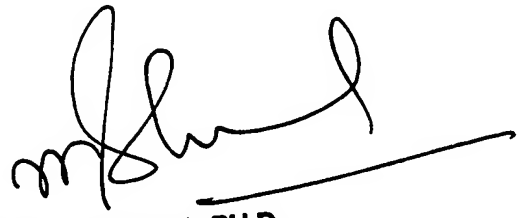

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